DETAILED ACTION

Response to Non-Final office action filed on August 28, 2008 is acknowledged. Claims 2, 9, 11, 24-28 are pending in this application. Claims 24-26 and 28 remain withdrawn from further consideration, as being drawn to nonelected species. Claims 2, 9, 11 and 27 are examined on the merits in this office action.

Declaration under 35 CFR 1.131

1. The declaration filed on August 28, 2008 under 37 CFR 1.131 has been considered but is ineffective to overcome the because the Curwen et al reference is a 102(b) reference not a 102(a) reference. The effective filing date of the instant application is September 02, 2004. The instant application claims a foreign priority to UNITED KINGDOM 0320806.3 filed on September 05, 2003. Since the Curwen reference was available November 2002, this is a 102(b) reference.

Maintained Rejection

35 U.S.C. 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 2, 9, 11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janus et al (US 2002/0055457) in view of Curwen et al (Poster EORTC-NCI-AACR, 2002), Nelson et al (BJU International, 2000, 85 (Suppl 2), 45-48) and Walczak et al (Expert Opin. Investig. Drugs, 2002).

5. The instant claims are drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl)phenyl)pyridine-3-sulfonamide and a bisphosphonate (pamidronic acid or a pharmaceutically acceptable salt thereof). The claims are additionally drawn to a pharmaceutical composition comprising a combination in association with a pharmaceutically acceptable diluent or carrier.

6. Janus et al disclose a method of inhibition of bone metastases including in cancer patients an effective amount of an endothelin ET-A receptor antagonist (see claim 1). The reference further teaches that the primary cancer is prostate cancer (see claim 4). Furthermore, the reference teaches that the method comprises administration of a therapeutic agent, bisphosphonate (see claim 9). The reference teaches that therapeutic agent (bisphosphonate) addition impedes net bone loss (see claim 8). Additionally, the reference teaches the pharmaceutical formulations, the compounds

may be administered orally, buccally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles (see paragraph [0115] and [0117]). This reads on claims 1 and 11. The difference between the reference and the instant claims is that the reference does not teach N-(3-methoxy-5-methylpyrazin-2-yl)-2-)4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide.

7. However, Curwen et al teach that ZD4054 (N-(3-methoxy-5-methylpyrazin-2-yl)-2-)4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide), a specific endothelin A receptor antagonist has utility in prostate cancer and metastatic bone disease (see poster, Figure 1, Results and Discussions). The reference further teaches that in vitro studies, ZD4054 is a high-affinity ligand for the human ET_A receptor, with a pIC_{50} value of 8.27, while ZD4054 had no measurable affinity for the ET_B receptor (see Results, In vitro radioligand binding studies). Additionally, the reference teaches that ZD4054 is a potent ETA receptor antagonist in vivo, producing a dose-related response (see Figure 2a and Results, Intravenous antagonist potency).

8. Nelson et al teach that the endothelin (ETs) are identical in all mammals and many higher vertebrates; the ET receptors are also very similar (see p. 45, left column, 2nd paragraph). Additionally, the reference teaches that every prostate cancer cell line tested produces ET-1 mRNA and protein (see p. 45, right column, 2nd paragraph). Furthermore, the reference teaches that using a selective ETA receptor antagonist, the abdominal constrictor response of mice to ET-1 was completely inhibited (see p. 46, right bottom paragraph and p. 47, top left paragraph).

9. Walczak et al teach that men with hormone-independent prostate cancer are at risk for skeletal morbidity (see p. 1742, 1st 2 lines of "4. Bone-targeted therapy"). The reference further teaches that bisphosphonates exert their action by inducing apoptosis of osteoclasts. Bisphosphonates have demonstrated in vitro inhibitory effect on breast and prostate cancer ell adhesion to bone, and a direct cellular effect in inhibiting tumor cell invasion and proteolytic activity of matrix metalloproteinases. Pamidronate disodium and zolendronic acid have also shown *in vitro* inhibition of prostate cancer cell growth (see p. 1742, section 4.1).

10. Therefore, it would have been obvious to one of ordinary skill in the art to combine the bisphosphonate and endothelin receptor antagonist. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in the treatment of prostate cancer, thus combining the two into a combination compound would show at least an additive effect. Additionally, the ordinary skilled artisans would be motivated to combine the teachings of the prior arts because Curwen et al teach that ZD4054 is a high-affinity ligand for the human ET_A receptor, while ZD4054 ha no measurable affinity for the ET_B receptor. Furthermore, Janus et al teach that bisphosphonate addition impeded bone loss (see claim 8). Therefore, since ZD4054 is selective for ET_A receptor, one would expect it to be active.

Response to Applicant's Arguments

11. In the previous remarks file on January 17, 2008, Applicant argued that "the presently claimed combination surprisingly produces a far greater than additive effect." Applicant further submitted Williams et al., Eur. J. Cancer Supplement 2006; 4(12):15, and argues that "in this research, the effect of ZD4054 alone, pamidronate alone and a combination of ZD4054 and pamidronate on the formation of bone metastases in a mouse model are compared...combining ZD4054 with pamidronate resulted in the surprising and unexpected finding that the combination actually prevented any detectable bone metastases such that no bone metastases were detected for the duration of the study." Same results were provided in Exhibit A.

In the remarks filed on August 28, 2008, Applicant argues that "Curwen et al is not prior art under 35 U.S.C. 102(a), since the claimed invention was invented by Applicant prior to the effective date of the reference. Applicant further argues that "claimed combination of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054) and a bisphosphonate resulted in the surprising and unexpected synergy in regard to inhibition of bone metastases in the treatment of prostate cancer…The synergy between ZD4054 and bisphosphonates was unexpected because bisphosphonates inhibit the activity of osteoclasts and are given to patients with prostate cancer not to treat the cancer, but as supportive care to relieve pain associated with bone metastases in prostate cancer."

12. Applicant's arguments have been fully considered but have not been found persuasive. The prior arts combined are *prima facie* obvious of the instant application.

Janus et al teach a method of inhibition of bone metastases by administering an effective amount of an endothelin ET-A receptor antagonist. Janus et al also teach that the method comprises administration of a therapeutic agent, bisphosphonate and this addition impedes net bone loss in treating prostate cancer. Curwen et al teach that ZD4054 is a specific endothelin A receptor antagonist and has utility in prostate cancer and metastatic bone disease. Nelson reference teaches that the endothelin (ETs) are identical in all mammals and many higher vertebrates, and the ET receptors are also very similar, and that every prostate cancer cell line tested produces ET-1 mRNA and protein. Walczak et al teach that bisphosphonates exert their action by inducing apoptosis of osteoclasts, and have demonstrated *in vitro* inhibitory effect on breast and prostate cancer cell adhesion to bone, and a direct cellular effect in inhibiting tumor cell invasion and proteolytic activity of matrix metalloproteinases. Walczak reference further teaches that pamidronate disodium and zoledronic acid have shown *in vitro* inhibition of prostate cancer cell growth.

Therefore, it would have been obvious to combine the teachings of the prior arts to produce a pharmaceutical composition comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-)4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulfonamide (ZD4054) and bisphosphonate (pamidronate), since Janus et al show that ET-A receptor antagonist and bisphosphonate addition impedes net bone loss and is for treating prostate cancer, and other references show the activity of ET-A receptor antagonist against prostate cancer and metastatic bone disease. Furthermore, Curwen et al teaches that ZD4054 is a potent ET_A receptor antagonist *in vivo* and has utility in prostate cancer and metastatic

bone disease (see Curwen reference). Furthermore, it would have been obvious to one of ordinary skill in the art to attack the disease from two different avenues to treat the disease. The references teach that ZD4054 (ET-A receptor antagonist) is used to treat prostate cancer and bisphosphonate is used to induce apoptosis of osteoclasts and inhibit the prostate cancer cell growth. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in treatment of prostate cancer, therefore, combining the two into a combination compound would show at least an additive effect. Further, since ZD4054 is selective for ET-A receptor, and Janus et al disclose that bisphosphonate addition impedes bone loss, there is a reasonable expectation that the addition of the two compounds into one composition would have an additive effect.

One of ordinary skill in the art would have been motivated to combine the ZD4054 and bisphosphonate to treat prostate cancer, since prior art independently teaches using bisphosphonate to treat prostate cancer (Walczak reference teaches that pamidronate disodium and zoledronic acid have shown *in vitro* inhibition of prostate cancer cell growth) and ET-A receptor antagonist (ZD4054) has been shown effective in treating prostate cancer (see Janus and Curwen). MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kekhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citation omitted) (Claims to a process of preparing a spray-

dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious). See also *In re Crockett*, 279 F.2d 274, 126, USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating case iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Ouadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). Therefore, one would be motivated to combine two known compounds each of which is taught by the prior art to be useful for the same purpose to form a third composition to be used for the very same purpose.

In regard to Applicant's argument that "Exhibit A (Williams Poster, Wednesday 8 November, 2006) shows that, the effect of ZD4054 alone, pamidronate alone and a combination of ZD4054 and pamidronate on the formation of bone metastases in a mouse model are compared...combining ZD4054 with pamidronate resulted in the surprising and unexpected finding that the combination actually prevented any detectable bone metastases such that no bone metastases were detected for the duration of the study." Applicant is directed to the graph showing the % mice with bone metastases. In this graph, the duration of the study was for 6 weeks. The vehicle/vehicle combination shows metastasis development after week 3; The ZD4054/vehicle show metastasis development after week 4; the vehicle/pamidronate show metastasis development after 5 weeks; ZD4054/pamidronate combination shows no bone metastasis up to 6 weeks. When the graph is looked at as a whole, the % metastasis

inhibition of vehicle/pamidronate compared to ZD4054/vehicle is very small. Furthermore, since the pamidronate had metastasis inhibitory effect up to week 5 and ZD4054 had metastasis inhibitory effect up to 4 weeks, the combination of ZD4054 and pamidronate would at least be additive and be expected to show no bone metastases up to 6 weeks. Since the study only shows the results up to 6 weeks, it is not known if bone metastasis would have resulted after 7, 8 or 9th week. Since ZD4054 alone had no bone metastasis up to 4 weeks, and pamidronate had no bone metastasis up to 5 weeks, when the two components were combined, one of ordinary skill in the art would expect that no bone metastasis would exist in week 6. In other words, one of ordinary skill in the art would have expected the mice administered the combination therapy to show no bone metastasis for longer duration than ZD4054 alone and pamidronate alone. This would be expected as an additive effect.

Applicant have argue that there is evidence to illustrate a greater than additive effect. However, Applicants have not provided what one would expect from the combination prior to filing of the instant application and how the results observed are indeed unexpected. The MPEP also states "a greater than additive effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage" See MPEP 716.02 (a). It is the position of the rejection that the combination of elements gave a predictable results. Therefore, one of ordinary skill in the art would have been

motivated to combine two known compounds for formation of a third compound for the treatment of same disease or disorder.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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